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Hemodynamic Effect of Angiotensin II Receptor Blockade in Postmenopausal Women on a High-Sodium Diet: A Double-Blind, Randomized, Placebo-Controlled Study

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ABSTRACT

BACKGROUND: Hypertension becomes increasingly prevalent after menopause. Postmenopausal women are more responsive to salt than premenopausal women, and they have been reported to develop marked renal vasoconstriction on a high-sodium diet.

OBJECTIVE: The aim of this study was to assess whether angiotensin II receptor blockade can restore a normal pattern of renal response to salt in postmenopausal women on a high-sodium diet. We also assessed segmental renal sodium handling in that population.

METHODS: Normotensive and hypertensive postmenopausal women not receiving hormone replacement therapy were enrolled in this prospective, double-blind, placebo-controlled, crossover study. They were assigned to receive irbesartan 150 mg or placebo for 6 weeks; the sequence in which they received irbesartan or placebo was randomized. During the last week of treatment, they received a high-sodium diet (250 mmol/d). Ambulatory blood pressure (ABP), glomerular filtration rate (GFR), and effective renal plasma flow (ERPF) were measured using sinistrin and para-aminohippurate clearances. Renal sodium handling was assessed by measuring endogenous lithium clearance on day 7 of the high-salt diet.

RESULTS: Nineteen women (mean age, 54.7 years; range, 43–72 years; 7 normotensive subjects [mean age, 53.4 years; range, 47–61 years] and 12 hypertensive subjects [mean age, 55.4 years; range, 43–72 years]) were included in the study. When the data for all 19 subjects were pooled, ABP was significantly lower with irbesartan than placebo both during the day (120 [3]/79 [2] vs 127 [3]/85 [2] mm Hg; both, $P < 0.01$) and at night (systolic BP, 107 [4] vs 111 [4] mm Hg [$P < 0.01$] and diastolic BP, 71 [2] vs 75 [2] mm Hg [$P < 0.05$]). Compared with placebo, irbesartan was not associated with a significant change in GFR in either the normotensive or the hypertensive women. When the data for all 19 subjects were pooled, irbesartan was associated with a significant increase in ERPF compared with placebo (372 [21] vs

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324 [18] mL/min · 1.73 m^2; $P < 0.05$). When the hypertensive and normotensive women were considered separately, the effect was more pronounced in the hypertensive women than in the normotensive women, but the changes did not reach statistical significance. When the data for all subjects were pooled, irbesartan was associated with a significant increase in daytime urinary sodium excretion compared with placebo (135 [13] vs 106 [13] μmol/min; $P < 0.05$) and a significant decrease at night (109 [13] vs 136 [19] μmol/min; $P < 0.05$). Fractional excretion of lithium (FE_{Li}), an inverse marker of proximal sodium reabsorption, increased significantly during the daytime with irbesartan compared with placebo (47% [6.5%] vs 35% [4.7%]; $P < 0.05$). At nighttime, FE_{Li} was significantly higher in the hypertensive subjects receiving irbesartan compared with placebo (43% [7.2%] vs 29% [6.5%]; $P < 0.05$). The fractional distal reabsorption of sodium did not change significantly with irbesartan compared with placebo.

CONCLUSIONS: The results from this study suggest that angiotensin II receptor blockade had a favorable impact on BP, renal hemodynamics, and renal sodium handling in these salt-replete postmenopausal women. Blockade of the renin-angiotensin system restored the normal pattern of renal response to high sodium intake in these women. (*Curr Ther Res Clin Exp.* 2008;69:467–479) © 2008 Excerpta Medica Inc.

KEY WORDS: blood pressure, lithium, renal hemodynamics, gender, angiotensin II receptor blockade.

INTRODUCTION

Cardiovascular disease is the leading cause of death in postmenopausal women.[1,2] Hypertension, a major cardiovascular risk factor, becomes more prevalent after menopause. Hypertension is more prevalent in postmenopausal women than in age-matched men.[3] Studies have reported that the renal response to stimuli, such as angiotensin II or lower body negative pressure (a means to decrease the venous return to the heart), that leads to activation of the sympathetic nervous system differs between men and women, with a smaller augmentation of filtration fraction (FF) and a blunted increase in intraglomerular pressure in women compared with men.[4–6] The renal response to salt among women has been reported to differ depending on whether they are in the luteal or follicular phase of their menstrual cycle and whether they are taking contraceptives or are in menopause.[7–9] In the luteal phase, the renal response to salt was characterized by significant renal vasodilation and marked salt excretion from distal nephrons compared to women during the follicular phase. We reported that after menopause women receiving a high-salt diet had a significant increase in blood pressure (BP), with increased proximal sodium reabsorption and marked and statistically significant renal vasoconstriction.[9] These findings suggested that with the onset of menopause, BP became salt-sensitive, a pattern that might be due to aging as well as to modification of the sex hormone profile; these results have been confirmed.[10]

The goal of the present study was to assess whether angiotensin II receptor blockade could restore a normal pattern of renal response to salt in postmenopausal women on a high-sodium diet. The primary end point was to measure ambulatory BP (ABP)

and renal hemodynamic changes induced by an angiotensin receptor blocker (ARB) in salt-replete postmenopausal women. The secondary end point was to assess segmental renal sodium handling in that population.

SUBJECTS AND METHODS

SUBJECTS

This was a prospective, double-blind, randomized, placebo-controlled, crossover study (**Figure**). The study included postmenopausal volunteers recruited among outpatients of University Hospital (Geneva, Switzerland) who were not receiving hormone replacement therapy (HRT). The participants were recruited using placards posted in the hospital that described the study. The women were classified as hypertensive (office BP ≥140/90 mm Hg and/or mean 24-hour ABP monitoring [ABPM] ≥125/80 mm Hg) or normotensive (office BP <140/90 mm Hg and/or mean 24-hour ABPM <125/80 mm Hg). All the women underwent natural menopause, defined as ≥1 year since their last menstruation. All were required to be nonsmokers and none could be taking antihypertensive drugs or any medication known to affect BP or renal function. Exclusion criteria were any cardiac or renal disease, diabetes, anemia, and use of aspirin, NSAIDs, or HRT.

At the initial visit, the subjects gave a full medical history (verified through medical records) and underwent a clinical examination. They were randomly assigned to receive either placebo or the ARB irbesartan 150 mg QD for 6 weeks, according to the crossover design. There was a 2-week washout period between the drug and placebo phases. Randomization of the sequence of placebo and active treatment periods was performed by a pharmacist who had no contact with the subjects or the clinicians. The random allocation scheme used a computer-generated random number list. The placebo and the active treatment, which were prepared by a pharmacist, were identical in appearance and were dispensed in identical bottles. The subjects received compensation for travel and meals. The clinicians were compensated for laboratory tests, ABPM devices, nurses' salaries, and travel to a medical congress. The study protocol was reviewed and approved by the institutional ethics committee (University Hospital) and all subjects provided written informed consent.

Tolerability to treatment was assessed at each visit by subject interview. The subjects were specifically asked if they had been suffering from fatigue, dizziness, or feelings of fainting when standing up.

CLINICAL INVESTIGATION

During the last week of therapy (week 6 of each treatment phase), subjects received a high-salt diet, which was achieved by adding 6 g/d of sodium chloride to their usual diet. On day 7 of both diet periods, 24-hour urine was collected separately during the day (8:00 AM–10:00 PM) and the night (10:00 PM–8:00 AM) to measure sodium excretion. Concomitantly, 24-hour BP was recorded using ABPM (Diasys, Physicor, Geneva, Switzerland). This device was validated by the British Hypertension Society and was rated B/B.[11] ABP was measured at 20-minute intervals during the day and every 60 minutes at night. The next day, patients were admitted to the hospital at 8:30 AM

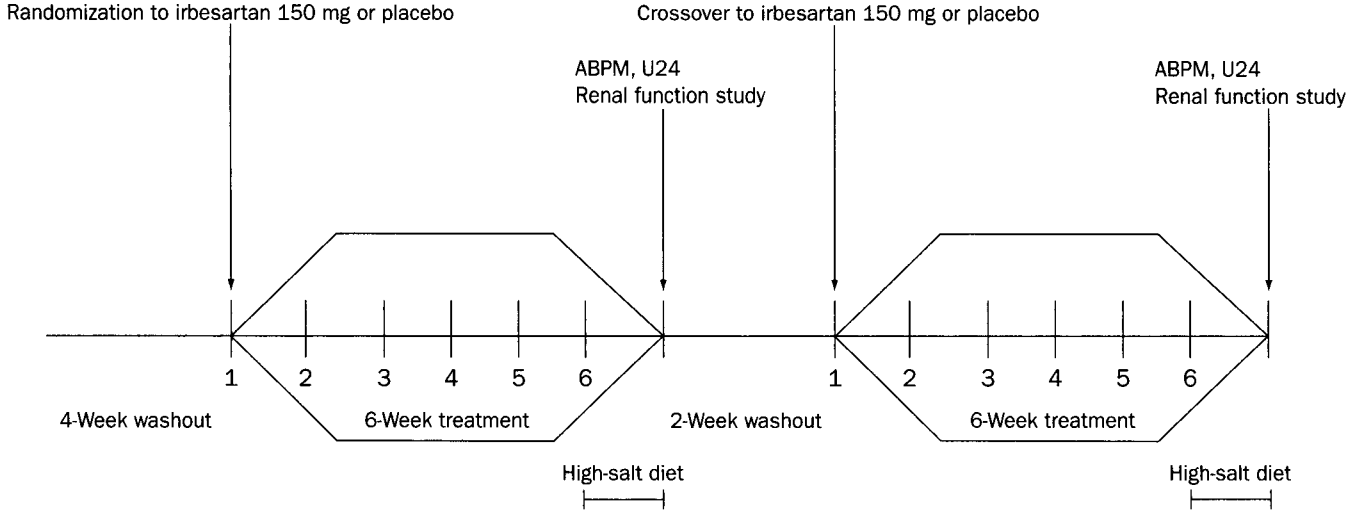

Figure. Study design. ABPM = 24-hour ambulatory blood pressure monitoring; U24 = 24-hour urine collection.

after an overnight fast to have their renal function measured. Renal hemodynamics were measured using sinistrin (an analogue of inulin) and para-amino-hippurate (PAH) clearances, as described previously.[12] After lying quietly for a 90-minute equilibration period in the supine position and administration of an oral water load of 5 mL/kg to ensure stable urine output, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured once in each of the two 90-minute clearance intervals.

ANALYTIC PROCEDURES

Sodium excretion was expressed as $U_{Na} \cdot V$ in mmol/d or μmol/min, where U_{Na} was the urinary sodium concentration and V was the urine volume expressed either in mL/24 hours or in mL/min. The FF was determined by dividing the GFR by effective renal plasma flow. Renal vascular resistance was calculated as follows:

$$MBP/(RBF/[1-Ht]),$$

where *MBP* was mean BP, *RBF* was renal blood flow, and *Ht* was hematocrit. Proximal renal sodium handling was assessed by measuring endogenous lithium in plasma and urine, as described previously,[12,13] and by the fractional excretion of lithium (FE_{Li}) and sodium (FE_{Na}) using the standard formula (FE_X = X clearance/GFR). The fractional distal reabsorption of sodium (ie, the percentage of the distally delivered sodium reabsorbed in the postproximal nephron segments) was calculated as follows:

$$([FE_{Li}-FE_{Na}]/FE_{Li}) \times 100.$$

Sinistrin* and PAH† were purchased directly from the manufacturers.

STATISTICAL ANALYSIS

All results were expressed as mean (SEM). Data were analyzed using a paired or unpaired *t* test for independent samples, when appropriate. The primary analysis was based on data from the per-protocol population. A modified intention-to-treat analysis was also performed and lead to the same results. The main comparison was made between placebo and irbesartan, with each subject being her own control. We calculated that 18 women would be needed to demonstrate a 10% difference in BP and FE_{Li} and a 20% change in ERPF, with an α of 0.05 and a β of 0.20.

RESULTS

We assessed 20 women for participation in the study. One of them successfully completed the screening, but withdrew prior to any study procedures. Therefore, the study included 19 postmenopausal white volunteers (mean age, 54.7 years; range, 43–72 years): 7 normotensive subjects (mean age, 53.4 years; range, 47–61 years) and

*Trademark: Inutest® (Laevosan Gesellschaft, Zürich, Switzerland).

†Manufactered by SERB Laboratoires Pharmaceutiques, Paris, France.

Table I. Baseline demographic and clinical characteristics of postmenopausal women enrolled in the study (N = 19). Data are mean (SEM) unless noted otherwise.

Characteristic	All (N = 19)	Normotensive (n = 7)	Hypertensive (n = 12)
Age, y	54.7 (4.2)	53.4 (3.8)	55.4 (4.1)
Range	43–72	47–61	43–72
Weight, kg	68.9 (2.5)	65.6 (2.5)	70.8 (3.7)
BMI, kg/m^2	25.9 (1.1)	24.3 (1.1)	26.8 (1.6)
Office BP, mm Hg	128 (4.1)/85 (4.4)	116 (3.1)/80 (3.4)	152 (6.0)/96 (4.2)*
Serum creatinine, μmol/L	68.3 (2.2)	69.2 (3.8)	67.8 (2.7)
FSH, U/L	50.2 (7.3)	58.3 (13.5)	45.4 (8.7)
Plasma estradiol, pg/mL	20.9 (6.4)	24.3 (15.7)	18.9 (5.1)

BMI = body mass index; BP = blood pressure; FSH = follicle-stimulating hormone.
*$P < 0.05$ versus normotensive subjects.

12 hypertensive subjects (mean age, 55.4 years; range, 43–72 years) (Table I). There were no statistically significant differences between the normotensive and the hypertensive women, except for baseline BP (116 [3.1]/80 [3.4] vs 152 [6.0]/96 [4.2] mm Hg; both, $P < 0.05$). No subjects were lost to follow-up.

BLOOD PRESSURE AND HEART RATE RESPONSES TO ANGIOTENSIN II RECEPTOR BLOCKADE

Daytime and nighttime ABPs and heart rates are presented in Table II. When the data for all 19 subjects were pooled, ABP was significantly lower with irbesartan than placebo both during the day (systolic BP, 120 [3] vs 127 [3] mm Hg; diastolic BP, 79 [2] vs 85 [2] mm Hg; both, $P < 0.01$) and at night (systolic BP, 107 [4] vs 111 [4] mm Hg; diastolic BP, 71 [2] vs 75 [2] mm Hg; $P < 0.01$ and $P < 0.05$, respectively). The effect of irbesartan on BP was observed essentially in the hypertensive women. A nocturnal physiologic decrease in systolic and diastolic BP was observed during both placebo and irbesartan treatment ($P < 0.01$, nighttime vs daytime). No significant effect was observed on heart rate.

RENAL HEMODYNAMIC RESPONSE TO ANGIOTENSIN II RECEPTOR BLOCKADE

The effects of irbesartan 150 mg on renal hemodynamics are presented in Table III. Compared with placebo, irbesartan was not associated with a significant change in GFR in either the normotensive or the hypertensive women. When the data for the 19 subjects were pooled, irbesartan was associated with a significant increase in ERPF compared with placebo (372 [21] vs 324 [18] mL/min · 1.73 m^2; $P < 0.05$). When the hypertensive and normotensive women were considered separately, the effect was more pronounced in the hypertensive subjects than in the normotensive subjects, but the changes did not reach statistical significance. FF was numerically lower with irbe-

Table II. Ambulatory blood pressure (BP) and heart rate responses to angiotensin II receptor blockade with irbesartan 150 mg/d compared with placebo in salt-replete postmenopausal women. Data are mean (SEM).

Variable/Group	All (N = 19)	Normotensive (n = 7)	Hypertensive (n = 12)
Daytime systolic BP, mm Hg			
Irbesartan 150 mg	120 (3)*	110 (4)	125 (3)†
Placebo	127 (3)	114 (4)	135 (4)
Daytime diastolic BP, mm Hg			
Irbesartan 150 mg	79 (2)*	75 (2)†	82 (2)*
Placebo	85 (2)	81 (3)	88 (2)
Nighttime systolic BP, mm Hg			
Irbesartan 150 mg	107 (4)*	95 (4)	115 (5)
Placebo	111 (4)	98 (7)	119 (5)
Nighttime diastolic BP, mm Hg			
Irbesartan 150 mg	71 (2)†	68 (2)	73 (2)†
Placebo	75 (2)	69 (4)	78 (2)
24-Hour heart rate, beats/min			
Irbesartan 150 mg	82 (2)	85 (3)	80 (2)
Placebo	81 (2)	82 (3)	81 (3)

*$P < 0.01$ versus placebo.
†$P < 0.05$ versus placebo.

sartan than placebo, but the difference did not reach statistical significance. Renal vascular resistance were significantly lower in women receiving irbesartan than placebo, assessing a renal vasodilation.

RENAL TUBULAR RESPONSE TO ANGIOTENSIN II RECEPTOR BLOCKADE

Consumption of a high-sodium diet was associated with a significant increase in body weight in women receiving placebo and irbesartan (1.01 [0.34] and 0.89 [0.31] kg, respectively; both, $P = 0.005$ vs baseline).

Table IV shows the $U_{Na} \cdot V$ and the FE_{Li} with placebo and irbesartan. When the data for all subjects were pooled, daytime $U_{Na} \cdot V$ was associated with a significant increase with irbesartan compared with placebo (135 [13] vs 106 [13] μmol/min; $P < 0.05$) and a significant decrease during the night (109 [13] vs 136 [19] μmol/min; $P < 0.05$), suggesting a change in the 24-hour distribution of sodium excretion. Twenty-four hour sodium balance remained constant in both phases.

When the data for all 19 subjects were pooled, FE_{Li}, an inverse marker of proximal sodium reabsorption, increased significantly during the daytime with irbesartan compared with placebo (47% [6.5%] vs 35% [4.7%]; $P < 0.05$). At nighttime, FE_{Li} was

Table III. Renal hemodynamic response to angiotensin II receptor blockade with irbesartan 150 mg compared with placebo in salt-replete postmenopausal women. Data are mean (SEM).

Variable/Group	All (N = 19)	Normotensive (n = 7)	Hypertensive (n = 12)
GFR, mL/min · 1.73 m^2			
Irbesartan 150 mg	60 (3.3)	58 (6.0)	62 (3.4)
Placebo	60 (2.4)	55 (4.3)	62 (2.6)
ERPF, mL/min · 1.73 m^2			
Irbesartan 150 mg	372 (21)*	349 (25)	383 (31)
Placebo	324 (18)	315 (27)	329 (25)
FF, %			
Irbesartan 150 mg	17.0 (0.1)	17.1 (1.6)	17.1 (1.3)
Placebo	20.0 (0.2)	17.8 (0.6)	20.6 (2.3)
RVR, dyne/cm^2			
Irbesartan 150 mg	12,148 (742)*	11,588 (725)	12,476 (1110)
Placebo	14,972 (1118)	13,720 (1092)	15,702 (1652)

GFR = glomerular filtration rate; ERPF = effective renal plasma flow; FF = filtration fraction; RVR = renal vascular resistance.
*$P < 0.05$ versus placebo.

significantly higher in the hypertensive subjects receiving irbesartan compared with placebo (43% [7.2%] vs 29% [6.5%]; $P < 0.05$). The fractional distal reabsorption of sodium did not change significantly with irbesartan compared with placebo.

DISCUSSION

Taken together, the results of the present study suggest that even on a high-sodium diet, an ARB administered to these postmenopausal women lowered 24-hour ABP, induced renal vasodilation with no change in GFR, and significantly reduced proximal sodium reabsorption. The effects on BP and proximal renal segmental reabsorption were observed mainly in the hypertensive women and to a lesser degree in the normotensive women. These findings suggest that ARB therapy in postmenopausal women restored the normal pattern of renal response to salt that was previously described in premenopausal women.[9]

All of the mechanisms responsible for the increase in BP after menopause have not been identified. The increased incidence of hypertension observed in postmenopausal women might be related to several mechanisms, including sodium retention or an altered BP response to sodium. We previously reported that the BP of menopausal women became salt-sensitive and that postmenopausal women respond to a high-salt diet with marked renal vasoconstriction, whereas in younger premenopausal women, a salt load–induced renal vasodilation.[9]

Table IV. Segmental renal sodium handling in salt-replete postmenopausal women during angiotensin II receptor blockade with irbesartan 150 mg compared with placebo. Data are mean (SEM).

Variable/Group	All (N = 19)	Normotensive (n = 7)	Hypertensive (n = 12)
Daytime $U_{Na} \cdot V$, μmol/min			
Irbesartan 150 mg	135 (13)*	126 (17)*	142 (19)
Placebo	106 (13)	90 (13)	115 (19)
Nighttime $U_{Na} \cdot V$, μmol/min			
Irbesartan 150 mg	109 (13)*	122 (19)	101 (17)
Placebo	136 (19)	151 (34)	127 (23)
Daytime FE_{Li}, %			
Irbesartan 150 mg	47 (6.5)*	45 (2.0)	39 (4.6)
Placebo	35 (4.7)	41 (5.5)	32 (6.5)
Nighttime FE_{Li}, %			
Irbesartan 150 mg	46 (6.1)	50 (1.2)	43 (7.2)*
Placebo	38 (5.4)	56 (5.5)	29 (6.5)
Daytime FDR_{Na}, %			
Irbesartan 150 mg	98 (1.0)	98 (0.4)	97 (0.6)
Placebo	97 (0.4)	98 (0.3)	98 (1.0)
Nighttime FDR_{Na}, %			
Irbesartan 150 mg	98 (0.4)	98 (0.3)	98 (0.5)
Placebo	96 (1.8)	98 (0.6)	94 (2.0)

U_{Na} = urinary sodium concentration; V = urine volume; FE_{Li} = fractional excretion of lithium; FDR_{Na} = fractional distal reabsorption of sodium.
*$P < 0.05$ versus placebo.

An increase in body weight occurring at menopause that may be linked to the change in sodium sensitivity in women has also been associated with a significant increase in ABP.[9] In this study, despite a high-salt diet, which was associated with an increase in body weight and has been reported to blunt the antihypertensive effect of blockers of the renin-angiotensin system,[14] irbesartan was associated with a significant decrease in BP. This effect was more pronounced in hypertensive subjects, suggesting that blockade of the renin system limited the salt-induced renal alterations that occurred in these postmenopausal women and restored BP salt sensitivity. Irbesartan has also been reported to reverse the nondipper BP profile, that is, the absence of the physiological decrease of BP during nighttime, in salt-sensitive hypertensive patients on a high-salt diet.[15] In our subjects, irbesartan was not associated with a change in the dipping profile of BP but was associated with a change in the day–night distribution of U_{Na}. Therefore, blockade of the renin-angiotensin system during menopause may be one way to restore BP salt sensitivity.

Before menopause, women might be protected against salt-sensitive hypertension by female sex hormones, which affect renal sodium excretion.[16] Changes in estrogen/androgen ratios at menopause could thus play a role in triggering elevated BP.[16] The possibility that androgens are important in the development of arterial hypertension in women should also be considered. Some data support this hypothesis, as male sex hormones contribute to the exacerbation of hypertension in animal models of spontaneously hypertensive rats (SHRs) by reducing the pressure-natriuresis curve.[17] The androgen-promoted exacerbation of BP appears to be mediated by the renin-angiotensin system.[3,18]

At menopause, the decrease in female sex hormones may also influence renal function. As discussed previously, a high-salt diet consumed for 1 week by menopausal women led to renal vasoconstriction, with a decrease in effective renal plasma flow and an increase in FF.[9] This renal response contrasts with the one observed in younger, premenopausal women,[7,19] suggesting again that endogenous female sex hormones play a role in mediating these alterations. In an animal model of postmenopausal hypertension in SHRs, along with the increase in BP observed in older rats, rats also had decreased GFR and renal plasma flow and increased renal vascular resistance compared with young females.[20] In these animals, blockade of the renin-angiotensin system resulted in marked attenuation of glomerular injury, a decrease in microalbuminuria, and reversal of renal hemodynamic changes.[18] At menopause, activation of the renin-angiotensin system might contribute to renal alterations independent of sodium intake.[21,22] Our findings in postmenopausal women are consistent with these experimental findings in animals, as angiotensin II receptor blockade restored the renal hemodynamic response to salt.

Data on the changes in renal sodium handling induced by menopause are scarce. In animal models, female sex hormones have been reported to protect against the development of Dahl hypertension mediated by increases in dietary sodium.[23] In some models of ovariectomized rats fed a high-sodium diet, hypertension developed, but reinstatement of a sodium chloride-deficient diet did not reverse the hypertension,[24] suggesting that removal of the female hormones predisposed the animals to hypertension that was initially sodium-dependent but might become sodium-independent with time. Androgens have been reported to increase tubular sodium and water reabsorption and to activate various vasoconstrictor systems in the kidney, including the renin-angiotensin and endothelin systems. Activation of these systems may lead to increased sodium reabsorption in the proximal and distal tubules. Moreover, experimental data suggest that androgens may directly upregulate the reabsorptive capacity of the renal proximal tubule and increase the volume reabsorptive rate, thereby enhancing extracellular volume and BP.[25] In our study, irbesartan decreased proximal sodium reabsorption in both normotensive and hypertensive postmenopausal women. With placebo as well as irbesartan, proximal sodium reabsorption was numerically higher in the hypertensive women than in the normotensive women, as indicated by a lower FE_{Li}. This was consistent with our initial observations in men suggesting that essential hypertension was associated with increased reabsorption of sodium in the proximal tubule, particularly on a high-salt diet.[26,27] The impaired ability of the

proximal tubule to regulate sodium excretion has also been associated with increased BP salt sensitivity.[26] The natriuretic response to irbesartan is probably due to blockade of the tubular effects of angiotensin II, which is known to act specifically at that segment of the nephron by promoting antinatriuresis. We reported that irbesartan, even at lower doses of 75 mg/d, increased U_{Na} in normotensive men.[28]

This observation may be of importance for the management of hypertensive postmenopausal women in order to provide them with the best prevention of cardiovascular and renal complications of hypertension. As there might be substantial gender-specific differences in the ABP response to antihypertensive treatments,[29] studies specifically designed to examine the gender aspect of preventing cardiovascular complications of hypertension with blockers of the renin-angiotensin system should be performed.

LIMITATIONS

To detect the effect of salt loading, we should have compared active treatment and placebo, not only on a high-salt diet, but also on a low-salt diet. The sample size used in this study may appear small; however, because each woman received active treatment and placebo (each being her own control), the statistical power of the study was calculated to be sufficient to detect a difference. Adherence to treatment and to the high-sodium diet was not monitored. Nevertheless, the statistical difference between the 2 treatments gives an indirect validation of our findings.

CONCLUSIONS

The results of this study suggest that angiotensin II receptor blockade had a favorable impact on BP, renal hemodynamics, and renal sodium handling in these salt-replete postmenopausal women. Blockade of the renin-angiotensin system restored the normal pattern of renal response to high sodium intake in these women.

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